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Biochimica et Biophysica Acta 1817 (2012) S40–S47

Contents lists available at SciVerse ScienceDirect

Biochimica et Biophysica Acta

journal homepage: www.elsevier.com/locate/bbabio

S5 Uncoupling Proteins

5P1

Analysis of uncoupling protein 2-deficient mice upon anaesthesia and sedation revealed a role for *UCP2* in locomotion

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General anaesthesia is associated with hypothermia, oxidative stress, and immune depression. Uncoupling Protein (UCP2) is a member of the mitochondrial carrier family present in many organs including the spleen, the lung and the brain. A role of UCP2 in the activation of the inflammatory/immune cells, in the secretion of hormones, and in the excitability of neurons by regulating the production of reactive oxygen species has been discussed. Because of the side effects of anaesthesia, we aimed to question the expression and the function of UCP2 during anaesthesia. Induction of anaesthesia with ketamine (20 mg/kg) or isoflurane (3.6 %) and induction of sedation with the α2 adrenergic receptor agonist medetomidine (0.2 mg/kg) stimulated infiltration of immune cells in the lung and increased UCP2 protein content in the lung, in both immune and non-immune cells. UCP2 content in the lung inversely correlated with body temperature decrease induced by medetomidine treatment. Challenge of the $Ucp2^{-/-}$ mice with isoflurane and medetomidine revealed an earlier behavioral recovery phenotype. Transponder analysis of body temperature and activity showed no difference between $Ucp2^{-/-}$ and control mice in basal conditions. However, upon an acute decrease of body temperature induced by medetomidine, $Ucp2^{-/-}$ mice exhibited increased locomotion activity. Together, these results show that UCP2 is rapidly mobilized during anaesthesia and sedation in immune cells, and suggest a role of UCP2 in locomotion.

doi:10.1016/j.bbabio.2012.06.116

5P2

Induction of uncoupling protein UCP3 by hydrogen peroxide increases survival in cardiac muscle cells: Implication of the antioxidant transcription factor Nrf2

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The physiological functions of UCP2 and UCP3 are still not established. However, extensive evidence supports the idea that these mitochondrial carrier proteins are involved in the control of reactive oxygen species (ROS) generation [1, 2]. Superoxide and the lipid peroxidation product hydroxynonenal have been shown to induce proton leak through UCPs [3, 4]. Since proton leak has the potential to modulate ROS generation, this suggests the existence of a feedback loop between ROS and proton leak mediated by UCPs [5]. Our aim was to examine the effect of hydrogen peroxide (H_2O_2) on UCP3 expression levels, the signalling pathways involved and the protective role of UCP3 against oxidative damage in HL-1 mouse cardiac muscle cells. Both UCP3 mRNA and protein significantly increased after 3 h treatment with H_2O_2 (0.3 mM), as determined by quantitative PCR and immunoblot, respectively. Likewise, H_2O_2 addition increased the nuclear accumulation of the antioxidant transcription factor Nrf2 (NF-E2-related factor 2), an essential regulator of the cellular redox homeostasis. Nrf2 interference by siRNA prevented H_2O_2-mediated UCP3 induction, and increased dichlorofluorescein diacetate (DCF-DA) fluorescence detection by flow cytometry, indicating an increase in ROS levels. ChIP assays allowed the identification of an antioxidant response element (ARE) within the UCP3 promoter that bound Nrf2 following H_2O_2 treatment. Cell death was determined by flow cytometry using propidium iodide (PI) fluorescence. H_2O_2 treatment induced cell death only at 24 h compared to untreated HL-1 cells. However, both siUCP3 and siNrf2 cells, showed an earlier increase on H_2O_2-induced PI fluorescence. Our results suggest that H_2O_2 treatment enhances UCP3 expression via Nrf2 in cardiac cells, and that this increase promotes survival in oxidatively challenged cells.

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